

## REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-27 are pending. The Examiner acknowledged that claims 10 and 14-15 are directed to allowable subject matter on page 10 of the Office Action.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. For example, limitations of independent claim 1 are incorporated into claims 7-8 and 23-24. Support is found for amending claim 12 at page 14, lines 2-3, of the specification; amending claim 19 at page 6, lines 4-9, of the specification; and amending claim 20 in accordance with Scheme 2 at page 12 of the specification. Entry of the amendments is requested to reduce issues on appeal.

### *35 U.S.C. 112 – Definiteness*

Claims 20-22 and 25-26 were rejected under Section 112, second paragraph, as being allegedly indefinite. Applicants traverse.

Claim 20 is amended to clarify that the derivative is associated with at least one organic compound. A derivative (D) is formed between (i) hyaluronic acid (HA) or a salt thereof and (ii) at least one heterocyclic compound selected from purine or pyrimidine (P). Thus, D is formed by a reaction between HA or a salt thereof and either purine or pyrimidine (P) (e.g.,  $D = HA + P$ ). A further characteristic of D is that it has at least one ionic bond between HA or a salt thereof and either purine or pyrimidine (P). According to a claimed process of claim 20, the derivative (D) is associated with at least one organic compound (NA) (e.g., natural amino acids, their oligomers, and their polymers). Therefore, according to the claimed process, D is associated with NA:  $D + NA = (HA + P) + NA$ .

Claims 21-22 and 25-26 are amended to recite active, positive steps required to practice the claimed methods.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

*35 U.S.C. 101 – Statutory Subject Matter*

Claims 21-22 and 25-26 were rejected under Section 101 as allegedly defining improper process claims. Applicants traverse because the amended claims define the claimed methods by their recited active, positive steps.

Withdrawal of the Section 101 rejection is requested because it is moot.

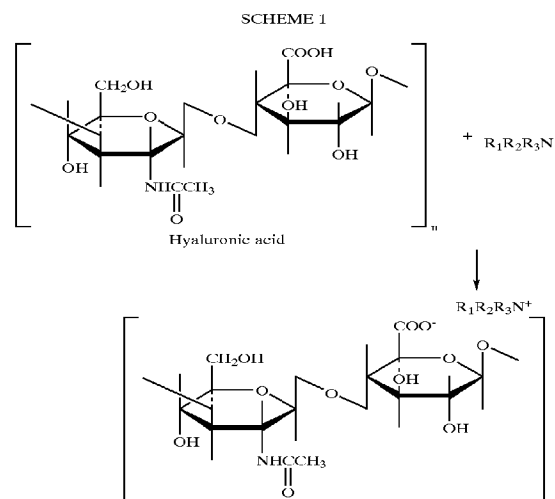
*35 U.S.C. 103 – Nonobviousness*

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See *id.* (“Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue”). The use of hindsight reasoning is impermissible. See *id.* at 1397 (“A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning”). Thus, a prima facie case of obviousness under Section 103(a) requires “some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.” *Kahn*, 78 USPQ2d at 1335; see *KSR*, 82 USPQ2d at 1396. A claim which is directed to a combination of prior art elements “is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *Id.* at 1396. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

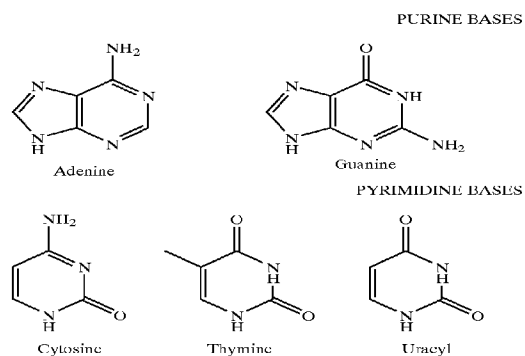
The present application relates to derivatives (D) between hyaluronic acid (HA) and at least one heterocyclic compound, particularly a nitrogenated base derived from purine and/or pyrimidine (P). See paragraph [0006]. Derivatives of purine are selected

from adenine and guanine, while derivatives of pyrimidine are selected from thymine and cytosine. See paragraph [0009]. The derivatives according to the present invention are characterized by bonds of ionic type that are labile and readily hydrolyzed under mild conditions, also by enzymatic activity. See paragraph [0003].

[0029] In practice, according to the present invention, hyaluronic acid is made to react with at least one purine and/or pyrimidine base chosen between the ones indicated above, in reaction conditions such as to form at least one bond of a ionic type between at least one “acid” centre of hyaluronic acid, such as for example a free carboxyl group in the form of an acid or in the form of a carboxylate salt, and at least one basic centre of the purine and/or pyrimidine base, which is also in the form of a free base or of an ammonium salt. The reaction scheme may in general be indicated as follows:



[0030] Where  $R_1R_2R_3N$  indicates generically at least one purine or pyrimidine base. The bases most commonly used have the following formulae:



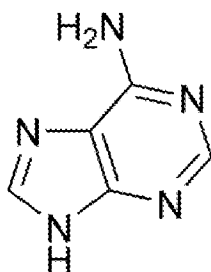
Guanine hyaluronate (I) (Example 1) and adenine hyaluronate (II) (Example 2) have been prepared by Applicants.

Claims 1-6, 9, 12-13, 19, 23-24 and 27 were rejected under Section 103(a) as allegedly unpatentable over FIDIA (EP 0 555 898 A2). Applicants traverse.

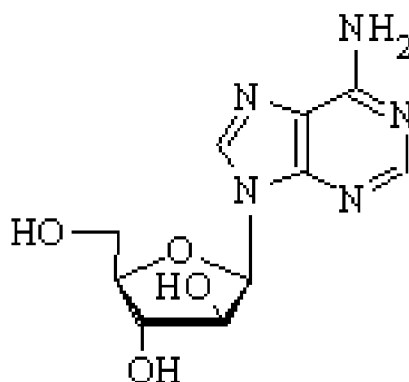
The Examiner cited FIDIA as allegedly disclosing a medicament comprising a partial or stoichiometrically neutral salt of hyaluronic acid with a basic pharmaceutically active substance. In FIDIA, the pharmaceutically active substance is identified as adenine arabinoside which is also called vidarabine, a well-known anti-viral drug active against herpes simplex and varicella zoster viruses (see Enclosures 1 and 2). Vidarabine is an analog of adenosine (i.e., a nucleoside consisting of a molecule of adenine attached to a ribofuranose moiety via a  $\beta$ -N<sub>9</sub>-glycosidic bond) with the D-ribose sugar (see Enclosure 3) replaced with D-arabinose (see Enclosure 4). Thus, FIDIA actually discloses a medicament comprising a pharmaceutically active molecule that can be, for example, hyaluronic acid and adenine arabinoside (i.e., vidarabine).

The Examiner alleged that one of ordinary skill in the art would have been motivated to prepare any compound suggested by FIDIA with a reasonable expectation that this compounds would have the utility suggested by FIDIA. That is to say that the skilled man would have been motivated to make a composition with hyaluronic acid and a pharmaceutically active molecule, known *per se* as having a pharmaceutical indication.

By contrast, the present invention relates to derivatives of hyaluronic acid that are formed between hyaluronic acid and a heterocyclic compound derived from purine and/or pyrimidine. See paragraph [0006]. Such heterocyclic compounds are not pharmaceutically active at all and do not have any pharmaceutical activity *per se* (see Enclosure 5). In particular, the present invention relates to a derivative where the purine and/or pyrimidine compounds are selected from adenine, guanine, thymine, cytosine, and uracyl. Adenine and guanine are preferred. Adenine has the following structure:



while adenine arabinoside, also called vidarabine, and cited in FIDIA, has the following structure:



From the above, it is evident that adenine and adenine arabinoside (i.e., vidarabine) have completely different structures and that they are completely different compounds.

Furthermore, adenine arabinoside is a pharmaceutically active compound, in which the adenine moiety is reacted and covalently linked to an arabinose sugar moiety, while adenine is not a pharmaceutically active compound, but it acts as a component of nucleic acids only when it is reacted and covalently linked to a ribose sugar moiety. The heterocyclic compounds of the present invention, which have at least one ionic bond to hyaluronic acid in accordance with the claimed invention (see claim 1) are not at all linked in any way to a sugar moiety. Therefore, the claimed derivatives are completely different from the adenine arabinoside disclosed in FIDIA.

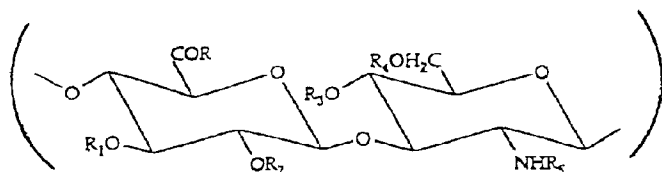
If one of ordinary skill in the art would have modified the compounds disclosed in FIDIA, maintaining the pharmaceutical activity of the compound would be expected. By contrast, purine and pyrimidine bases are linked by ionic bond(s) to hyaluronic acid in accordance with the present invention, but they are not pharmaceutically active and do not have any pharmaceutical activity if taken alone. FIDIA discloses, on the contrary, that hyaluronic acid must be associated with a compound that already possesses a pharmaceutical activity. Therefore, there is no reason provided for modifying FIDIA's disclosure to link hyaluronic acid with a molecule having no pharmaceutical activity at all by ionic bond(s).

Applicants' claimed invention is patentable over FIDIA.

Claims 1-9, 11-12, 16-18 and 23-24 were rejected under Section 103(a) as allegedly unpatentable over Bellini et al. (WO 00/01733). Applicants traverse.

The Examiner cited Bellini as allegedly disclosing amides of hyaluronic acid having the general formula indicated at page 3, lines 10-15. Amides are obtained by reacting an amine with a free carboxyl group of hyaluronic acid or by reacting an acid with a deacylated amino group of hyaluronic acid (page 4, lines 8-11). Claim 1 requires an amide compound of hyaluronic acid having the following general formula:

1. An amide of hyaluronic acid or a derivative thereof which comprises at least one repetitive unit of the following general formula:



wherein:

R = NR<sub>6</sub>R<sub>7</sub>, or alcoholic group of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, OH, O-, alcoholic group of hyaluronic acid, amino group of deacylated hyaluronic acid;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> = H, SO<sub>3</sub><sup>-</sup>, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, -CO- (CH<sub>2</sub>)<sub>2</sub>-COOY; Y = negative charge, or H;

R<sub>5</sub> = -CO-CH<sub>3</sub>, H, SO<sub>3</sub><sup>-</sup>, acyl group derived from a carboxylic acid of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, acylic group of hyaluronic acid;

R<sub>6</sub> = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

R<sub>7</sub> = is H or a aliphatic, aromatic, arylaliphatic, cycloaliphatic, or heterocyclic group, substituted or unsubstituted;

wherein at least one of R or R<sub>5</sub> forms an amide group.

According to the above, Bellini's amide of hyaluronic acid always has at least one amide group which is an R or R<sub>5</sub> moiety. Further, Bellini discloses at page 7, lines 3-6, that:

Moreover, the amide derivatives can be obtained by reaction of carboxyl or deacylated nitrogen of hyaluronic acid or a derivative thereof with an amine or with a pharmaceutically active acid respectively, or they may be salified or simply associated with said compounds.

When an amide derivative corresponding to an R<sub>5</sub> moiety is to be obtained, the acylated nitrogen of hyaluronic acid must be deacylated and then reacted with a pharmacologically active acid. See page 10, line 19, to page 11, line 3. It is therefore clear that the R<sub>5</sub> moiety corresponds to an amide derivative where the acylating moiety originally present on the hyaluronic acid molecule has been replaced with a suitable moiety deriving from a pharmacologically active acid.

The Examiner also referred to claim 8 of WO 00/01733, where a salification product is disclosed, which depends from claims 1 to 7, where the above amide derivative is described. Thus claim 8 relates to a salification product between the amide derivative according to claim 1 (and thus characterized by the already mentioned R and R<sub>5</sub> moieties) and pharmacologically active substances. In accordance with page 7, lines 3-6, (see above), it is clear that the amide derivatives may be salified or simply associated with pharmacologically active acids.

As already discussed above, the present invention does not permit any structural modification of the hyaluronic acid. No covalent bonds are formed between the hyaluronic acid and the purine or pyrimidine base. No amide derivatives are formed reacting the acylated nitrogen of hyaluronic acid. Since no amide derivatives as described in Bellini are formed, the salification product according to the present invention does not correspond to Bellini's salification product. See claim 8 of WO 00/01733.

By contrast, the present invention relates to a salification product between hyaluronic acid (as such) and a purine or pyrimidine base. Bellini discloses the preparation of an amide derivative of hyaluronic acid and its subsequent salification with a pharmacologically active acid.

Applicants' claimed invention is patentable over Bellini et al.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

*Conclusion*

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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